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# Prepregnancy plant-based diets and the risk of gestational diabetes mellitus: a prospective cohort study of 14,926 women

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## ABSTRACT

**Background:** Emerging evidence suggests beneficial impacts of plant-based diets on glucose metabolism among generally healthy individuals. Whether adherence to these diets is related to risk of gestational diabetes mellitus (GDM) is unknown.

**Objectives:** We aimed to examine associations between plant-based diets and GDM in a large prospective study.

**Methods:** We included 14,926 women from the Nurses' Health Study II (1991–2001), who reported  $\geq 1$  singleton pregnancy and without previous GDM before the index pregnancy. Prepregnancy adherence to plant-based diets was measured by an overall plant-based diet index (PDI), healthful plant-based diet index (hPDI), and unhealthful plant-based diet index (uPDI) as assessed by FFQs every 4 y. Incident first-time GDM was ascertained from a self-reported physician diagnosis, which was previously validated by review of medical records. We used log-binomial models with generalized estimating equations to calculate RRs and 95% CIs for associations of PDIs with GDM.

**Results:** We documented 846 incident GDM cases over the 10-y follow-up among 20,707 pregnancies. Greater adherence to the PDI and hPDI was associated with lower GDM risk. For the PDI, the multivariable-adjusted RR (95% CI) comparing the highest and lowest quintiles (Q5 compared with Q1) was 0.70 (0.56, 0.87) ( $P_{\text{trend}} = 0.0004$ ), and for each 10-point increment was 0.80 (0.71, 0.90). For the hPDI, the RR (95% CI) of Q5 compared with Q1 was 0.75 (0.59, 0.94) ( $P_{\text{trend}} = 0.009$ ) and for each 10-point increment was 0.86 (0.77, 0.95). After further adjustment for prepregnancy BMI, the associations were attenuated but remained significant: for the PDI, the RR (95% CI) for each 10-point increment was 0.89 (0.79, 1.00)

and the corresponding RR (95% CI) was 0.89 (0.80, 0.99) for the hPDI. The uPDI was not associated with GDM.

**Conclusions:** Our study suggests that greater prepregnancy adherence to a healthful plant-based diet was associated with lower risk of GDM, whereas an unhealthful plant-based diet was not related to GDM risk. *Am J Clin Nutr* 2021;114:1997–2005.

**Keywords:** overall plant-based diet, healthful plant-based diet, unhealthful plant-based diet, dietary patterns, gestational diabetes mellitus

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Supplemental Figure 1 and Supplemental Tables 1–7 are available from the “Supplementary data” link in the online posting of the article and from the same link in the online table of contents at <https://academic.oup.com/ajcn/>.

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Abbreviations used: aHEI, Alternative Healthy Eating Index; aMED, Alternative Mediterranean diet; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; GDM, gestational diabetes mellitus; hPDI, healthful plant-based diet index; NHS II, Nurses' Health Study II; PDI, overall plant-based diet index; Q, quintile; T2D, type 2 diabetes; uPDI, unhealthful plant-based diet index.

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## Introduction

Gestational diabetes mellitus (GDM), which affects 4%–9% of all US pregnancies on average (1), is at the center of the vicious cycle of diabetes begetting diabetes. It has been linked to not only adverse obstetrics and perinatal outcomes (2), but also greater long-term risk of cardiometabolic disorders in both mothers and their offspring (3, 4) after the index pregnancy. It is therefore crucial to identify modifiable risk factors for the prevention of GDM. Although the conventional focus has been on risk factors during pregnancy, accumulating data support the importance of prepregnancy exposures in the development of GDM (2, 5). However, prospective studies of prepregnancy modifiable factors, especially related to habitual dietary patterns and GDM, remain sparse (2, 5).

Emerging evidence suggests that adherence to several healthy dietary patterns before pregnancy, such as the Mediterranean diet, Healthy Eating Index, and Dietary Approaches to Stop Hypertension (DASH) diets, is related to a lower risk of GDM (6, 7). Recently, plant-based diets, which primarily differ from the above *a priori*-defined healthful dietary patterns by emphasizing the consumption of higher proportions of all plant foods and lower proportions of all animal foods in the diet, have grown in popularity. In particular, the 2015–2020 Dietary Guidelines for Americans recommended a plant-based diet, particularly rich in healthy plant foods, as one of the dietary patterns for general health and prevention of chronic diseases (8). Plant-based diets have been associated with lower risks of type 2 diabetes (T2D) (9) and cardiovascular disease (CVD) (10). Plausible mechanisms for the inverse association between plant-based diets and cardiometabolic diseases include promoting weight loss/maintenance, enhanced glycemic control, improved lipid profiles, decreased inflammation, and improved gut microbiota (9–11). Some of these traits have been implicated in the development of GDM as well (2). As such, plant-based diets may be beneficial for the prevention of GDM. However, unique pathophysiological features related to pregnancy including placental factors (e.g., exosomes and hormones) can influence insulin resistance and  $\beta$ -cell function which may predispose certain women to an elevated risk of GDM, independently of adiposity (2). Whether plant-based diets shown to benefit T2D can be extended to GDM is not known. Moreover, plant-based diets are becoming increasingly popular in the United States, especially among women (12). Therefore, it becomes an important public health priority to examine whether prepregnancy plant-based diets may be efficacious for the prevention of metabolic complications in pregnancy.

In the present study, we sought to assess the associations of plant-based diets, both overall and when defined according to the quality of plant foods, with incident GDM in a large prospective cohort of women of reproductive age. We hypothesized that a plant-based diet, especially one that emphasizes intake of healthy plant foods, would be associated with a lower risk of incident GDM.

## Methods

### Study population

The Nurses' Health Study II (NHS II) started in 1989 with the recruitment of 116,678 female registered nurses aged 25–44 y. These participants received a biennial questionnaire which

asked about disease outcomes and lifestyle behaviors, such as smoking status and medication use (13). Response rates for each questionnaire cycle were >90%. In the current study, we included participants who reported  $\geq 1$  singleton pregnancy lasting >6 mo. The first FFQ was administered in 1991, hence we set this year as the baseline and only included pregnancies that occurred after the return of the 1991 questionnaire. GDM was last ascertained on the 2001 questionnaire, at which point most participants had passed their reproductive age. We excluded pregnancies if the participant reported a prior GDM diagnosis, which could lead to changes in diet and lifestyle during subsequent pregnancies. We also excluded pregnancies if the participant reported a prior diagnosis of CVD, diabetes, or cancer (other than nonmelanoma skin cancer); had not returned any FFQ before the pregnancy; had >70 FFQ items missing; or reported improbable total energy intakes (<600 or >3500 kcal/d). After exclusions, we included 20,707 incident pregnancies among 14,926 NHS II participants (**Supplemental Figure 1**). This study was approved by the institutional review board of the Brigham and Women's Hospital and Harvard TH Chan School of Public Health. Informed consent was implied by the participant's return of a completed questionnaire. Data described in the manuscript, code book, and analytic code can be made available upon request via the application process described at <https://www.nurseshealthstudy.org/researchers>.

### Dietary assessment

Dietary data were collected using a previously validated semiquantitative FFQ beginning in 1991 and subsequently administered every 4 y (e.g., in 1995 and 1999) (14). For each food item, participants were asked to report the frequencies with which they consumed a specific portion of each of the 131 food or food group items during the past year. The reproducibility and validity of food and dietary pattern measurements in the NHS II have been described previously (15, 16). For the current study, we excluded these questionnaires if administered when women were pregnant. This way, it ensured all reported diet represented diet before pregnancy. We calculated an overall plant-based diet index (PDI), a healthful plant-based diet index (hPDI), and an unhealthful plant-based diet index (uPDI) to assess the degree of adherence to overall, healthful, and unhealthful plant-based diets, respectively. The methods of constructing the 3 indexes have been described previously (17). Briefly, we created 18 food groups according to nutrient and culinary similarities to calculate each of the PDIs (**Supplemental Table 1**). We further classified these 18 food groups into 3 larger categories: healthy plant food groups, unhealthy plant food groups, and animal food groups. The categorization of healthy and less healthy plant foods was according to the most recent empirical evidence (8, 18–24). Specifically, healthy plant food groups included 7 food groups: whole grains, fruits, vegetables, nuts, legumes, vegetable oils, and tea/coffee; unhealthy plant food groups included 5 food groups: fruit juices, sugar-sweetened beverages, refined grains, potatoes, and sweets/desserts; and animal food groups included 6 food groups: animal fats, dairy, eggs, fish/seafood, meat including poultry and red/processed meat, and miscellaneous animal-based foods. We ranked each one of the 18 food groups into quintiles and each quintile was assigned a score ranging from 1 to 5. For the overall PDI, higher intakes of healthy and unhealthy plant

food groups were given higher scores, whereas higher intakes of animal food groups were given lower scores. For the hPDI, we gave healthy plant food groups positive scores, and unhealthy plant food groups and animal food groups reverse scores. For the uPDI, unhealthy plant food groups received positive scores, whereas healthy plant food groups and animal food groups received reverse scores. We summed the quintile scores of each of the 18 food groups to obtain the overall indexes, which can theoretically range from 18 through 90. A higher score on the PDI was reflective of a higher intake of plant foods and/or a lower intake of animal foods; a higher score on the hPDI was reflective of a higher intake of healthy foods and/or a lower intake of unhealthy foods and animal foods; and a higher score on the uPDI was reflective of a higher intake of unhealthy plant foods and/or a lower intake of healthy plant foods and animal foods. Because the fatty acid composition of margarines has changed over time, from high in *trans*-fat before and during the 1990s to be high in unsaturated fats at present, the health implications of margarines at present are largely different from those in the past, including the 1990s when dietary data relevant to the present study were collected (17). As such, to evaluate associations of PDIs with GDM risk that can be applied to the population nowadays, we did not include data on margarines when deriving each of the PDIs and instead adjusted for their intakes in the multivariable model.

### Outcome assessment

Incident first-time GDM was the primary outcome. NHS II participants reported incident physician-diagnosed GDM on each biennial questionnaire up to 2001. For participants who reported >1 pregnancy lasting >6 mo within a 2-y questionnaire period, GDM diagnosis was attributed to the first pregnancy. In a prior validation study among a subsample of NHS II participants, 94% of self-reported GDM diagnosis was confirmed by medical record review (25), whereas, among women who had a pregnancy uncomplicated by GDM, 83% reported a glucose loading test, and 100% reported frequent urine screening in pregnancy, consistent with a high degree of GDM surveillance (25). The National Diabetes Data Group criteria (26) for diagnosing GDM were widely adopted during the study follow-up period, between 1991 and 2001.

### Assessment of covariates

Participants reported their ethnicity and family history of diabetes in 1989. They reported their height, weight, parity, and smoking status in each biennial questionnaire (e.g., in 1991, 1993, and 1995). Based on height and weight, we calculated prepregnancy BMI. As such, prepregnancy BMI data used in the current analyses were collected before or at the same time as each FFQ cycle (in 1991, 1995, and 1999). Total physical activity was ascertained by inquiring about the frequency of engaging in common recreational activities in 1991, 1997, and 2001, from which metabolic equivalent hours per week were derived.

### Statistical analysis

We calculated cumulatively updated averages for PDI, hPDI, and uPDI, before pregnancy for participants at each time period

to reduce intraindividual variation and to better represent long-term habitual prepregnancy diet. For instance, the 1991 PDI was used for the follow-up between 1991 and 1995, the average of the 1991 and 1995 PDIs was used for the follow-up between 1995 and 1999, and the average of the 1995 and 1999 PDIs was used for the follow-up between 1999 and 2001.

Participant characteristics at baseline in 1991 were presented by quintiles of PDI, hPDI, or uPDI in 1991. We also examined the correlations of PDIs with several a priori–defined healthy dietary indexes such as the Alternative Mediterranean diet (aMED) index, the Alternative Healthy Eating Index (aHEI), and the DASH index.

We used log-binomial models with generalized estimating equations to estimate RRs and 95% CIs of first incident GDM in relation to quintiles of PDIs. Generalized estimating equations allowed us to account for correlations among repeated observations (pregnancies) contributed by a single participant (27). In model 1, we adjusted for age and parity (0, 1, 2, and  $\geq 3$  pregnancies lasting  $\geq 6$  mo). In model 2, we in addition adjusted for ethnicity (white, African American, Hispanic, Asian, other, and missing/not reported), family history of diabetes (yes, no), cigarette smoking (never, past, current, and missing/not reported), physical activity (quintiles), alcohol intake (g/d; 0, 1–14,  $\geq 15$ ), margarine intake (servings/d; quintiles), and total energy intake (kcal/d; quintiles). In model 3, we in addition adjusted for updated prepregnancy BMI ( $\text{kg/m}^2$ ; <23.0, 23.0–24.9, 25.0–26.9, 27.0–29.9, 30.0–34.9,  $\geq 35.0$ , and missing). Prepregnancy BMI was entered into the model separately because it could serve as both a confounder and a mediator of the associations between plant-based diets and GDM risk. All of the adjusted variables were treated as time-varying covariates that were updated during each 2-y questionnaire cycle. We tested for linear trend across quintiles of PDIs by treating the median value of each quintile of PDI, hPDI, or uPDI as a continuous variable in the models. We in addition examined the association between a 10-point increment in each index and GDM risk.

We conducted stratified analyses according to other major risk factors for GDM. These included baseline age (<35 compared with  $\geq 35$  y), parity (nulliparous compared with parous), family history of diabetes (no compared with yes), physical activity (less than the median compared with equal to the median or greater), and prepregnancy BMI (<25 compared with  $\geq 25$ ). *P* values for interactions were derived from the cross-product interaction term coefficient [continuous PDIs (per 10-point increment)  $\times$  binary variable] added to the main-effects multivariable model (model 3). Given the potential for multiple testing, we set the statistical level for significance for these interactions at 0.003 (0.05/15) according to Bonferroni correction. To assess the robustness of our findings, we conducted several sensitivity analyses based on the fully adjusted model (model 3). First, we performed analyses using only the most recent data for plant-based diets before pregnancy, instead of the cumulative averaged data of plant-based diets, as the exposure variables. Second, we examined the associations of prepregnancy plant-based diets at baseline in 1991 only with risk of GDM. Third, we examined the associations of consuming an overall and a healthful plant-based diet while allowing for the inclusion of fish and yogurt which have previously been shown to be associated with lower cardiometabolic risk (28–32). For this, we created 2 variations of the PDI and hPDI by in addition assigning intake of fish or

**TABLE 1** Age-standardized characteristics of the study population in 1991 according to quintiles of plant-based diet indexes before pregnancy, Nurses' Health Study II<sup>1</sup>

|                                  | PDI           |               | hPDI        |               | uPDI          |               |
|----------------------------------|---------------|---------------|-------------|---------------|---------------|---------------|
|                                  | Q1            | Q5            | Q1          | Q5            | Q1            | Q5            |
| Participants, <i>n</i>           | 3250          | 3221          | 3172        | 2926          | 3198          | 3286          |
| Mean PDI score                   | 46.1 ± 3.1    | 63.2 ± 3.3    | 44.6 ± 3.5  | 64.5 ± 3.7    | 45.3 ± 3.6    | 65.5 ± 3.5    |
| Age, y                           | 31.6 ± 3.2    | 32.3 ± 3.3    | 31.3 ± 3.1  | 32.6 ± 3.3    | 32.6 ± 3.3    | 31.2 ± 3.2    |
| White                            | 91.9          | 93.5          | 92.4        | 93.6          | 95.0          | 90.6          |
| Family history of diabetes       | 12.3          | 9.5           | 11.3        | 10.7          | 11.5          | 10.6          |
| Nulliparous                      | 40.8          | 35.4          | 30.1        | 47.1          | 36.5          | 37.0          |
| Current smoking                  | 12.6          | 7.9           | 11.0        | 8.7           | 9.5           | 10.2          |
| Alcohol, g/d                     | 3.2 ± 6.0     | 3.2 ± 4.8     | 2.9 ± 5.2   | 3.2 ± 4.9     | 4.2 ± 5.9     | 2.3 ± 4.7     |
| BMI, kg/m <sup>2</sup>           | 23.8 ± 4.8    | 22.6 ± 3.8    | 23.7 ± 4.8  | 22.8 ± 3.5    | 23.5 ± 4.1    | 23.1 ± 4.5    |
| Physical activity, MET h/wk      | 19.6 ± 24.7   | 28.9 ± 35.7   | 18.4 ± 23.7 | 31.7 ± 36.8   | 30.3 ± 36.3   | 18.3 ± 24.1   |
| Total energy intake, kcal/d      | 1515 ± 472    | 2151 ± 531    | 2172 ± 540  | 1540 ± 464    | 2108 ± 522    | 1568 ± 502    |
| Food group intake, servings/d    |               |               |             |               |               |               |
| Total healthy plant foods        | 5.8 ± 2.9     | 11.8 ± 4.2    | 6.7 ± 3.2   | 10.8 ± 4.3    | 12.7 ± 4.0    | 5.0 ± 2.2     |
| Fruits                           | 0.7 ± 0.6     | 1.8 ± 1.2     | 0.9 ± 0.7   | 1.6 ± 1.1     | 1.9 ± 1.1     | 0.7 ± 0.6     |
| Vegetables                       | 2.2 ± 1.4     | 4.4 ± 2.3     | 2.5 ± 1.5   | 4.0 ± 2.4     | 4.8 ± 2.3     | 1.8 ± 1.1     |
| Whole grains                     | 0.9 ± 0.9     | 2.2 ± 1.3     | 1.2 ± 1.0   | 1.9 ± 1.3     | 2.2 ± 1.3     | 0.9 ± 0.8     |
| Nuts                             | 0.1 ± 0.2     | 0.4 ± 0.4     | 0.2 ± 0.3   | 0.3 ± 0.4     | 0.4 ± 0.4     | 0.1 ± 0.2     |
| Legumes                          | 0.2 ± 0.2     | 0.5 ± 0.4     | 0.3 ± 0.3   | 0.4 ± 0.4     | 0.5 ± 0.4     | 0.2 ± 0.2     |
| Vegetable oils                   | 0.2 ± 0.3     | 0.4 ± 0.5     | 0.2 ± 0.3   | 0.4 ± 0.5     | 0.5 ± 0.5     | 0.1 ± 0.2     |
| Tea and coffee                   | 1.4 ± 1.6     | 2.1 ± 1.8     | 1.4 ± 1.6   | 2.2 ± 1.8     | 2.4 ± 1.8     | 1.2 ± 1.4     |
| Total unhealthy plant foods      | 3.2 ± 1.9     | 6.0 ± 2.6     | 6.5 ± 2.6   | 2.9 ± 1.6     | 4.1 ± 2.1     | 5.0 ± 2.6     |
| Fruit juices                     | 0.4 ± 0.7     | 1.2 ± 1.1     | 1.0 ± 1.0   | 0.5 ± 0.8     | 0.8 ± 0.9     | 0.7 ± 0.9     |
| Refined grains                   | 1.2 ± 0.8     | 2.0 ± 1.1     | 2.1 ± 1.2   | 1.2 ± 0.8     | 1.5 ± 1.0     | 1.6 ± 1.1     |
| Potatoes                         | 0.4 ± 0.4     | 0.6 ± 0.4     | 0.8 ± 0.5   | 0.3 ± 0.2     | 0.5 ± 0.3     | 0.6 ± 0.4     |
| Sugar-sweetened beverages        | 0.4 ± 0.9     | 0.6 ± 0.9     | 1.0 ± 1.2   | 0.1 ± 0.4     | 0.3 ± 0.5     | 0.8 ± 1.1     |
| Sweets and desserts              | 0.8 ± 0.9     | 1.6 ± 1.2     | 1.7 ± 1.3   | 0.7 ± 0.8     | 1.1 ± 0.9     | 1.3 ± 1.2     |
| Total animal foods               | 4.6 ± 2.1     | 4.5 ± 2.0     | 5.7 ± 2.2   | 3.6 ± 1.7     | 5.9 ± 2.2     | 3.4 ± 1.6     |
| Animal fat                       | 0.2 ± 0.5     | 0.1 ± 0.3     | 0.3 ± 0.6   | 0.1 ± 0.2     | 0.3 ± 0.5     | 0.1 ± 0.4     |
| Red/processed meat               | 0.4 ± 1.2     | 0.4 ± 1.1     | 0.6 ± 1.0   | 0.3 ± 1.1     | 0.5 ± 1.1     | 0.4 ± 1.2     |
| Poultry                          | 0.3 ± 0.9     | 0.3 ± 0.9     | 0.3 ± 0.8   | 0.3 ± 0.9     | 0.4 ± 1.0     | 0.2 ± 0.8     |
| Dairy                            | 2.4 ± 1.5     | 2.5 ± 1.5     | 2.9 ± 1.6   | 2.1 ± 1.4     | 3.3 ± 1.6     | 1.8 ± 1.3     |
| Eggs                             | 0.2 ± 0.2     | 0.2 ± 0.2     | 0.3 ± 0.2   | 0.1 ± 0.1     | 0.2 ± 0.2     | 0.1 ± 0.2     |
| Fish and seafood                 | 0.3 ± 0.2     | 0.3 ± 0.3     | 0.3 ± 0.2   | 0.3 ± 0.3     | 0.4 ± 0.3     | 0.2 ± 0.2     |
| Miscellaneous animal-based foods | 0.2 ± 0.8     | 0.2 ± 0.6     | 0.3 ± 0.8   | 0.1 ± 0.5     | 0.3 ± 0.8     | 0.1 ± 0.5     |
| Margarine intake                 | 0.5 ± 0.6     | 0.7 ± 0.8     | 0.7 ± 0.8   | 0.5 ± 0.6     | 0.7 ± 0.8     | 0.5 ± 0.7     |
| Total fiber, g/d                 | 15.1 ± 5.0    | 21.1 ± 5.6    | 14.5 ± 3.3  | 23.0 ± 6.5    | 21.0 ± 5.8    | 15.0 ± 4.1    |
| Vitamin C, mg/d                  | 227.9 ± 320.0 | 272.3 ± 259.4 | 198 ± 211.9 | 306.9 ± 343.5 | 277.4 ± 286.9 | 217.4 ± 282.1 |

<sup>1</sup>*n* = 14,926 participants. Values are mean ± SD for continuous variables and percentages for dichotomous variables. All values except age are standardized to the age distribution of the study population. Age-standardized percentages might not be equal to percentages directly calculated by numerator and denominator in each PDI quintile. hPDI, healthful plant-based diet index; MET, metabolic equivalent; PDI, overall plant-based diet index; Q, quintile; uPDI, unhealthy plant-based diet index.

yogurt positive scores. Fourth, we also examined the association of consuming a healthful plant-based diet while scoring fruit juice positively. Last, to assess whether any observed associations were mainly driven by a single food group, we created modified PDIs by individually excluding each of the 18 food groups from the indexes and assessed associations of each of the modified indexes and risk of GDM with further adjustment for intake of the excluded food.

All statistical analyses were performed with SAS software, version 9.4 (SAS Institute). Statistical tests were 2-sided and a *P* value < 0.05 was considered statistically significant.

## Results

At baseline (in 1991), women with a higher PDI score, indicating greater adherence to an overall plant-based diet, were older, less likely to be nulliparous, and less likely to be current smokers (Table 1). They also tended to have a lower BMI, greater physical activity, and higher consumption of total energy, plant

foods, fiber, and vitamin C. Women with a higher hPDI score were older, more likely to be nulliparous, less likely to be current smokers, had a lower BMI, engaged in more physical activity, and consumed less total energy, unhealthy plant foods, and animal foods, but more healthy plant foods, fiber, and vitamin C. Women of greater uPDI score were generally younger and engaged in less physical activity, and consumed more unhealthy plant foods, as well as less healthy plant foods, fibers, vitamin C, and animal foods (Table 1, Supplemental Table 2). The PDIs were modestly to moderately correlated with aMED, aHEI, and DASH, with the following Pearson correlation coefficients: 0.68 between aHEI and hPDI; 0.29 between PDI and hPDI (Supplemental Table 3). Furthermore, Supplemental Table 3 also shows the overlap between the top quintiles of the PDIs and aMED, aHEI, and DASH. For example, 28.9% and 58.9% of women in the top quintile of PDI and hPDI were also in the highest quintile of aHEI, respectively (Supplemental Table 3).

During the 10 y of follow-up, we documented 846 incident first-time GDM cases. Adherence to the PDI was associated



**TABLE 2** RRs (95% CIs) for GDM according to plant-based diet indexes before pregnancy, Nurses' Health Study II<sup>1</sup>

|                                    | Q1         | Q2                | Q3                | Q4                | Q5                | P-trend | Per 10-point increment |
|------------------------------------|------------|-------------------|-------------------|-------------------|-------------------|---------|------------------------|
| Overall plant-based diet index     |            |                   |                   |                   |                   |         |                        |
| Median score                       | 47.0       | 51.0              | 54.0              | 57.3              | 62.0              |         |                        |
| GDM/pregnancies                    | 211/4431   | 159/3628          | 163/3849          | 166/4524          | 147/4275          |         |                        |
| Model 1                            | 1.0 (Ref.) | 0.92 (0.75, 1.12) | 0.90 (0.73, 1.10) | 0.79 (0.64, 0.96) | 0.72 (0.59, 0.89) | 0.0007  | 0.83 (0.74, 0.92)      |
| Model 2                            | 1.0 (Ref.) | 0.92 (0.75, 1.13) | 0.89 (0.72, 1.09) | 0.76 (0.61, 0.94) | 0.70 (0.56, 0.87) | 0.0004  | 0.80 (0.71, 0.90)      |
| Model 3                            | 1.0 (Ref.) | 0.96 (0.79, 1.18) | 0.94 (0.77, 1.15) | 0.84 (0.68, 1.04) | 0.83 (0.66, 1.03) | 0.05    | 0.89 (0.79, 1.00)      |
| Healthful plant-based diet index   |            |                   |                   |                   |                   |         |                        |
| Median score                       | 45.0       | 50.5              | 54.0              | 58.0              | 64.0              |         |                        |
| GDM/pregnancies                    | 210/4364   | 162/4067          | 151/3528          | 179/4792          | 144/3956          |         |                        |
| Model 1                            | 1.0 (Ref.) | 0.80 (0.65, 0.97) | 0.81 (0.66, 0.99) | 0.70 (0.57, 0.85) | 0.64 (0.52, 0.79) | <0.0001 | 0.80 (0.73, 0.88)      |
| Model 2                            | 1.0 (Ref.) | 0.85 (0.70, 1.04) | 0.87 (0.71, 1.08) | 0.77 (0.63, 0.95) | 0.75 (0.59, 0.94) | 0.009   | 0.86 (0.77, 0.95)      |
| Model 3                            | 1.0 (Ref.) | 0.86 (0.71, 1.05) | 0.91 (0.74, 1.13) | 0.82 (0.67, 1.01) | 0.79 (0.63, 1.00) | 0.046   | 0.89 (0.80, 0.99)      |
| Unhealthful plant-based diet index |            |                   |                   |                   |                   |         |                        |
| Median score                       | 46.0       | 52.0              | 55.5              | 59.0              | 65.0              |         |                        |
| GDM/pregnancies                    | 181/4323   | 152/3955          | 161/4087          | 163/3871          | 189/4471          |         |                        |
| Model 1                            | 1.0 (Ref.) | 0.92 (0.75, 1.14) | 0.98 (0.80, 1.21) | 1.05 (0.85, 1.29) | 1.08 (0.88, 1.32) | 0.30    | 1.09 (0.99, 1.19)      |
| Model 2                            | 1.0 (Ref.) | 0.91 (0.74, 1.13) | 0.96 (0.77, 1.19) | 1.00 (0.81, 1.24) | 0.99 (0.80, 1.23) | 0.86    | 1.05 (0.94, 1.16)      |
| Model 3                            | 1.0 (Ref.) | 0.93 (0.76, 1.15) | 0.99 (0.80, 1.23) | 1.03 (0.83, 1.27) | 1.03 (0.83, 1.29) | 0.59    | 1.06 (0.96, 1.18)      |

<sup>1</sup>*n* = 14,926 participants. RRs and 95% CIs were calculated based on log-binomial models with generalized estimating equations. Model 1: age and parity (0, 1, 2, ≥3). Model 2: Model 1 + ethnicity (white, African American, Hispanic, Asian, others), family history of diabetes (yes, no), cigarette smoking (never, past, current), physical activity (metabolic equivalent h/wk; quintiles), alcohol intake (g/d; 0, 1–14, ≥15), total energy intake (kcal/d; quintiles), and margarine intake (servings/d; quintiles). Model 3: Model 2 + prepregnancy BMI (kg/m<sup>2</sup>; <23.0, 23.0–24.9, 25.0–26.9, 27.0–29.9, 30.0–34.9, ≥35.0, missing). GDM, gestational diabetes mellitus; Q, quintile.

with a lower GDM risk after multivariable adjustment (model 2) [RR for highest compared with lowest quintiles (Q5 compared with Q1): 0.70; 95% CI: 0.56, 0.87;  $P_{\text{trend}} = 0.0004$ ]. The adjusted RR per 10-point increment was 0.80 (95% CI: 0.71, 0.90). Further adjustment for prepregnancy BMI attenuated the association (RR for Q5 compared with Q1: 0.83; 95% CI: 0.66, 1.03;  $P_{\text{trend}} = 0.05$ ; for per 10-point increment: 0.89; 95% CI: 0.79, 1.00) (model 3). Likewise, after multivariable adjustment (model 2), an inverse association was observed between the hPDI and GDM (RR for Q5 compared with Q1: 0.75; 95% CI: 0.59, 0.94;  $P_{\text{trend}} = 0.009$ ; for per 10-point increment: RR: 0.86; 95% CI: 0.77, 0.95), which was modestly attenuated after further adjustment for prepregnancy BMI (model 3) (RR for Q5 compared with Q1: 0.79; 95% CI: 0.63, 1.00;  $P_{\text{trend}} = 0.046$ ; for per 10-point increment: RR: 0.89; 95% CI: 0.80, 0.99) (Table 2). The uPDI was not significantly associated with GDM (RR for Q5 compared with Q1: 1.03; 95% CI: 0.83, 1.28;  $P_{\text{trend}} = 0.59$ ; for per 10-point increment: RR: 1.06; 95% CI: 0.96, 1.18) (Table 2).

No significant effect modifications were identified by other major risk factors for GDM. Associations of PDI, hPDI, and uPDI with GDM risk were in general consistent across subgroups characterized by age at the index pregnancy (<35 compared with ≥35 y), parity (nulliparous compared with parous), family history of diabetes (no compared with yes), physical activity (less than the median compared with equal to the median or greater), and prepregnancy BMI (<25 compared with ≥25) (all *P* values for interaction > 0.003) (Figure 1). In particular, we found that the associations for the PDIs did not significantly differ by parity (nulliparous compared with parous). Further, we observed similar associations of the PDIs with GDM based on the most recent dietary data before the index pregnancy or baseline diet in 1991 instead of the cumulative average dietary data (Supplemental Table 4). Furthermore, when the PDI and hPDI were modified to score fish/seafood or yogurt intake positively, the associations

were not materially altered (Supplemental Table 5). Moreover, the association remained similar when the hPDI was modified to score fruit juice consumption positively (Supplemental Table 6). In addition, when we excluded the 18 food groups 1 at a time from the PDIs, and adjusted for the excluded food group, we observed that the associations of the modified PDIs were attenuated irrespective of excluding any of the 18 food groups, and the magnitude of attenuation was similar. However, among these excluded food groups, higher intakes of whole grains and nuts were associated with lower risk of GDM, whereas higher intakes of potatoes and red and processed meat were associated with higher risk of GDM (Supplemental Table 7). These results indicated that the beneficial associations could mainly be driven by higher intake of whole grains and nuts and lower intake of potatoes and red and processed meat.

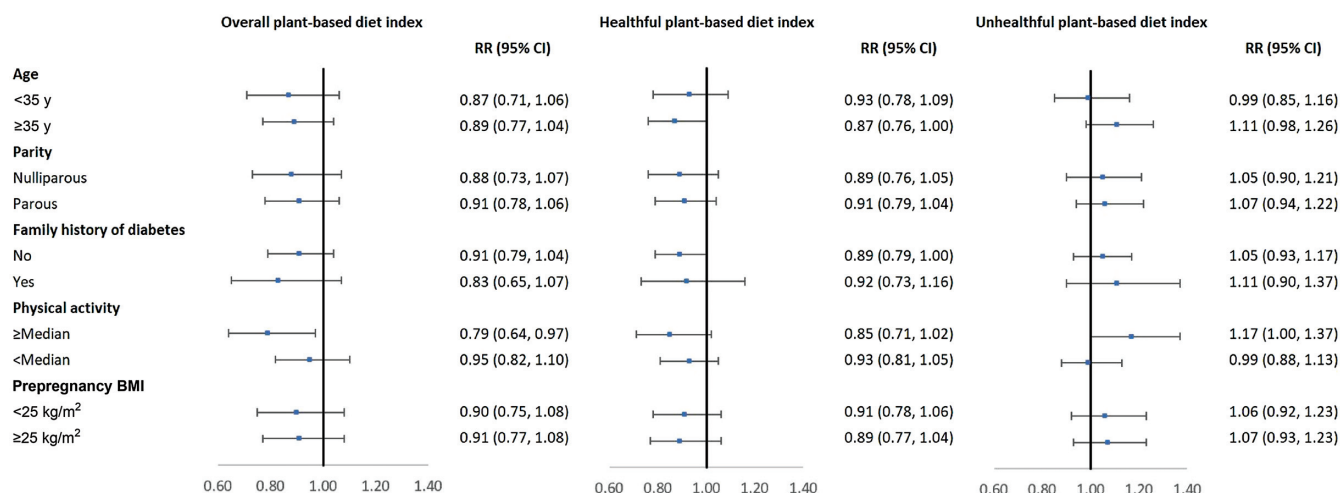
## Discussion

### Principal findings

In the present study, we observed inverse associations of adherence to overall and healthful plant-based diets with GDM incidence. The association of the hPDI was attenuated but remained significant even after controlling for prepregnancy BMI, whereas that of the PDI was marginally significant after in addition adjusting for prepregnancy BMI. We did not observe an association between an unhealthful plant-based diet and incident GDM.

### Results in relation to other studies and implications of findings

To our knowledge, our study represents the largest investigation to date into the relation between prepregnancy plant-based diets and incident GDM. Our findings are generally consistent



**FIGURE 1** Subgroup analyses of the associations between plant-based diets and gestational diabetes risk per 10-point increment in each index score. Risks and 95% CIs were calculated based on log-binomial models with generalized estimating equations. Models were adjusted for age, parity (0, 1, 2, ≥3), ethnicity (white, African American, Hispanic, Asian, others), family history of diabetes (no, yes), cigarette smoking (noncurrent, current), physical activity (metabolic equivalent h/wk; quintiles), alcohol intake (g/d; 0, 1–14, ≥15), total energy intake (kcal/d; quintiles), margarine intake (servings/d; quintiles), and prepregnancy BMI (kg/m<sup>2</sup>; <23.0, 23.0–24.9, 25.0–26.9, 27.0–29.9, 30.0–34.9, ≥35.0, missing). *P* values for heterogeneity were derived from the cross-product interaction term coefficient (continuous plant-based diet score × binary variable) added to the main-effects multivariable model. Given the potential for multiple testing, the statistical level for significance for these interactions was set at 0.003 (0.05/15) according to Bonferroni correction. All *P* values for these interaction terms were not statistically significant (all *P* values > 0.003).

with the inverse associations between plant-based diets and incident T2D among nonpregnant individuals. For instance, a recent meta-analysis demonstrated a 23%–30% lower risk of T2D comparing higher adherence to overall and healthful plant-based diets with lower adherence among predominantly middle-aged men and women (9). In addition, our findings on prepregnancy adherence to healthful plant-based diet are consistent with those of previous studies focusing on prepregnancy adherence to other healthy dietary patterns (6, 33, 34). For instance, in our previous study, we observed that compared with the participants in the lowest quartile, the participants in the highest quartile of the aMED, aHEI, and DASH indexes had a 24%, 34%, and 46% lower risk of GDM, respectively (6). Moreover, an Australian population-based prospective cohort study observed that prepregnancy adherence to the aMED was associated with a 15% lower risk of developing GDM for each SD increase in the score (33).

A plant-based diet, particularly one rich in healthy plant-based foods, may represent a viable alternative approach in addition to other popular healthful diets, such as the Mediterranean and DASH diets, in reducing GDM risk (6). Indeed, we only observed low to moderate correlations of the hPDI with each of the aMED, aHEI, and DASH indexes. The hPDI focuses on the quality of plant foods and scores all animal foods negatively, whereas aMED, aHEI, and DASH assign positive scores not only to healthy plant foods but also to healthy animal foods (e.g., fish and dairy). Interestingly, in the sensitivity analyses after modifying the PDI and hPDI to score high-quality animal foods (e.g., fish and yogurt) positively, we found similar associations of the PDI and hPDI with a lower GDM risk. Such findings might have important public health implications; an overall or healthful plant-based diet may not require a complete elimination of animal foods, but instead it could be achieved largely through reducing intake of low-quality animal foods (e.g., red and processed meat),

which may be more easily adapted by women of reproductive age. In turn, such modified PDIs were still different from other known healthy dietary patterns (e.g., aMED, aHEI, and DASH diets) by highlighting the quantity and quality of plant-based foods. Moreover, to shift toward an overall or healthful plant-based diet is to improve food sustainability because plant foods require fewer natural resources than animal foods (35). Given these points, our findings may help to inform dietary guidelines for women of reproductive age. However, we should avoid overinterpretation of the findings, because complete exclusion of animal-based foods may result in a lack of some essential nutrients such as iron or vitamin B-12, which may lead to impaired fetal growth and development (36).

### Possible interpretations of findings

There are several potential mechanisms that may interpret our findings. A plant-based diet, particularly one rich in healthy plant-based foods, tends to emphasize more intake of minimally processed plant foods, such as whole grains, fruits, vegetables, and nuts, leading to an increased intake of dietary fibers, plant protein, unsaturated fats, and antioxidants such as vitamin C (28, 37). These components have been linked to less adiposity, improved insulin sensitivity, reduced inflammation, and improved gut microbiome composition (38–40), and hence lead to the reduced GDM risk (2). Indeed, we previously observed that prepregnancy dietary fiber intake, in particular cereal and fruit fiber (41), and plant protein, especially from nuts, were inversely associated with GDM risk (42, 43). On the other hand, lower intake of animal foods may also contribute to the inverse association between healthful plant-based diet and GDM risk. Prepregnancy intakes of red and processed meat, animal protein, saturated fat, and heme iron have been associated with increased

risk of GDM through various pathways, such as weight gain, oxidative stress, and increased inflammation (42, 44).

Given that BMI represents a pathway through which plant-based diets may affect GDM risk (45, 46), controlling for it might have resulted in an underestimation of the overall associations of PDIs with GDM risk. At the same time, BMI could also be a confounder, for which statistical adjustment gives a more accurate estimate of the independent association between plant-based diets and GDM. Indeed, in the present study, we observed that the association of a healthful plant-based diet with GDM was attenuated but remained significant after further adjustment for prepregnancy BMI. Furthermore, we observed that the association was generally consistent across nonobese and obese women.

### Strengths and potential limitations

Our present study has several strengths. The use of a large prospective cohort of reproductive-age women afforded high statistical power to analyze the associations between prepregnancy adherence to plant-based diets and incident GDM and potential heterogeneity across specific subgroups. Dietary assessments, using a well-validated dietary questionnaire, were conducted before the index pregnancy, which avoids the potential recall bias that could occur after a participant has already become pregnant. For most participants, diet and lifestyle were assessed repeatedly before pregnancy, which could have helped to better capture long-term exposures and reduce dietary misclassifications. Several limitations deserve mentioning. First, we did not have information on diet during pregnancy. However, when comparing with the role of dietary factors during pregnancy in the development of GDM, cumulative evidence tends to support the importance of prepregnancy dietary factors (2). Therefore, although it is likely that the diet during prepregnancy and pregnancy is correlated (47), dietary habits after becoming pregnant may not substantially confound the associations we observed. Nevertheless, future research is still needed to explore the independent and joint effects of PDIs before and during pregnancy in relation to GDM risk. Second, although our repeated dietary data were measured ~20 y ago, except margarine, the major components of most plant foods and animal foods were similar with those nowadays (17); therefore, like the results of other dietary patterns (e.g., the Mediterranean diet) and GDM in the NHS II (6), the results of this current study still have important public health implications for dietary behaviors nowadays. Third, the majority of participants in our cohort were health professionals of European ancestry with a similar educational and socioeconomic background, and therefore the observed associations may limit the generalizability of our findings to women of other ethnic or socioeconomic groups. Evidence has indicated that populations of higher socioeconomic status may consume higher amounts of healthy plant-based foods, such as whole grains, vegetables, and fruit, whereas low-income populations may generally consume more unhealthy plant-based foods, such as refined grains, because healthy plant-based foods generally cost more (48, 49). In turn, replications of our findings in other ethnic populations with more diverse socioeconomic status are warranted to verify our findings. However, the use of a homogeneous cohort as in the present study can help to reduce some sources of unmeasured confounding of the association between plant-based diets and

GDM risk. Fourth, owing to the observational nature of our study, residual or unmeasured confounding cannot be ruled out. However, the dose-response relation, broad consistency across multiple subgroups, and supporting mechanisms from interventional studies suggest that it is less likely that the associations we observed were solely due to confounding or chance. Despite this, future research is warranted to address the true causal associations of prepregnancy overall and healthful plant-based diets with GDM risk. Fifth, diagnosis of GDM was based on self-report; however, as mentioned previously, the vast majority of cases were confirmed via medical record review and the surveillance for GDM in this cohort of health professionals was very high. The rate of GDM (5.7%) in this study was in the upper range of the usual reported rates (range: 3%–6%) in the United States according to the National Diabetes Data Group criteria during the same period (50). This rate may reflect the high rate of screening in this cohort, which included health professionals. Nevertheless, we acknowledge that using the National Diabetes Data Group criteria for GDM diagnosis may have identified women with more severe hyperglycemia as GDM than if using other criteria such as the Carpenter and Coustan criteria or the International Association of Diabetes and Pregnancy Study Groups criteria. Furthermore, we did not have information to gauge the severity of GDM in most of our participants. Last, our study did not assess fetal outcomes. Plant-based diets, particularly a restrictive one with minimal consumption of animal foods, may lead to suboptimal or deficient intakes of certain micronutrients such as iron or vitamin B-12, which may lead to impaired fetal growth and development (36).

### Conclusion

In conclusion, our study observed that greater adherence to a plant-based diet before pregnancy, particularly when being enriched with healthy plant foods, among a population of predominantly Caucasian health professionals, was associated with a lower risk of GDM. These findings not only further highlight the importance of diet and lifestyle before pregnancy for the prevention of GDM but also may provide an alternative dietary approach that may reduce the population burden of GDM. Future studies in other populations are warranted to confirm our findings.

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The authors' responsibilities were as follows—ZC, FQ, GL, FBH, and CZ: designed the study; JEC and FBH: were involved in data collection; ZC: conducted the analyses; ZC and FQ: drafted the manuscript; CZ: supervised the project; ZC and CZ: are the guarantors of this work; and all authors: contributed to the interpretation of the results and revision of the manuscript and read and approved the final manuscript. The authors report no conflicts of interest.

### Data Availability

Data described in the manuscript, code book, and analytic code can be made available upon request pending application and approval from the Nurses' Health Study II as described at <https://www.nurseshealthstudy.org/researchers> (contact e-mail: [nhsaccess@channing.harvard.edu](mailto:nhsaccess@channing.harvard.edu)).



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